Cell Stem Cell
Commentary

From Stem Cells to Grandmother Cells: How Neurogenesis Relates to Learning and Memory

Tracey J. Shors[1,2,*]
[1]Department of Psychology
[2]Center for Collaborative Neuroscience
Rutgers University, 152 Frelinghuysen Road, Piscataway, NJ 08854, USA
*Correspondence: shors@rutgers.edu
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Neurogenesis contributes thousands of new neurons each day to the hippocampus of the adult brain. Their production is influenced by numerous internal and external environmental factors, but their survival is especially sensitive to processes of learning. This commentary considers how learning enhances the survival of neural stem/progenitor cell progeny and what these new neurons might do once they are rescued from death.

The adult brain possesses what appear to be neural stem cells. These cells produce progeny that ultimately differentiate into neurons in the hippocampal formation. Nearly a decade ago, it was reported that the new neurons may be connected to the processes of learning and memory (Gould et al., 1999). For centuries, scientists have been struggling to discover how we learn and remember. As such, the neuronal processes whereby we acquire and retain new information remain, in large part, a mystery. This failure is not for any lack of trying. Scientists have long been perusing the brain in hopes of finding that elusive "engram," the term used to signify the location of a memory in the brain. Of course, we now know that memories are not stored in just one circumscribed location and that learning occurs via a dynamic process of neuronal activity within and between structures; but exactly how and where that activity occurs are still largely undetermined.

In the mid 1900s, psychologist Karl Lashley conducted a series of experiments in which he lesioned or damaged parts of the cerebral cortex in rodents. Afterwards, the animals were placed in various learning situations to determine whether they could learn and, if so, what they could learn (Lashley, 1950). In the end, he concluded that the engram, such as it is, was distributed throughout the brain and thus required activity within and communication among multiple brain regions. This idea was referred to as the theory of "mass action." He also proposed that if one brain region was damaged, other regions could take over, a process known then as "equipotentiality," and embraced more recently as "compensatory mechanisms." The idea that learning was distributed throughout large chunks of neuronal tissue was later challenged by the idea that processes of learning and especially those of memory were confined to relatively discrete brain structures. Taken a step further, this idea implied that a group of cells could encode the memory of a complex object or concept. Taken to the extreme, memories could be encoded within individual cells. In the 1960s, the neurophysiologist Jerome Lettvin coined the term "grandmother cell" to refer to a cell in the brain that would encode the memory of each person's grandmother. As such, this cell would only respond when seeing or thinking of your grandmother and no one else's grandmother or person. Obviously, other cells would be used to encode the memory of your mother, father, etc.

In Search of the Grandmother Cell

The idea that one cell might encode the memory of your grandmother may not be as far fetched as it seems. There is actually a significant amount of data indicating that neurons respond preferentially to specific objects or even concepts (Gross et al., 1969). In fact, a recent study reported evidence for cells that responded to an image of Jennifer Aniston, with or without Brad Pitt (Quiroga et al., 2005). However, the existence of cells that fire selectively to stored images does not mean that they are necessarily responsible for holding a memory in storage and does not in any way explain the complicated processes of learning; nor would their existence resolve the debate about whether learning is localized or distributed. Nonetheless, from these ideas, we have come to appreciate and to some extent accept the idea that processes of learning require neuronal activity within specific regions of the brain.

In their search for the engram, most neuroscientists have focused their attention on the hippocampal formation (Figure 1). Neurons in this brain region are especially responsive to ongoing experience and are necessary for several types of learning and some memory processes. But why is the hippocampus involved in these processes? What might it be doing, and are some cells more involved than others? Perhaps we might answer these questions if we asked them in a slightly different way—i.e., what does the hippocampus do that most other structures do not? Does it possess some special property that makes it especially amenable to processing these types of associations and complex forms of learning? Actually, the hippocampus does possess a rather unusual feature; it can generate new neurons, a process referred to as neurogenesis. Historically, neurogenesis was thought to cease at birth or soon thereafter and thus was not considered integral to processes of learning or memory. However, we now know that the mammalian brain produces thousands of new cells in the hippocampus each day, most of which will differentiate into neurons, provided that they survive (Cameron et al., 1993; Eriksson et al., 1998; Kempermann, 2005). We also know that these cells are more likely to survive if they exist in the hippocampus of an animal that has learned (Gould et al., 1999; Waddell and Shors, 2008). However, not all learning will rescue these neurons from death. The types of learning that do so are relatively limited—and are not necessarily

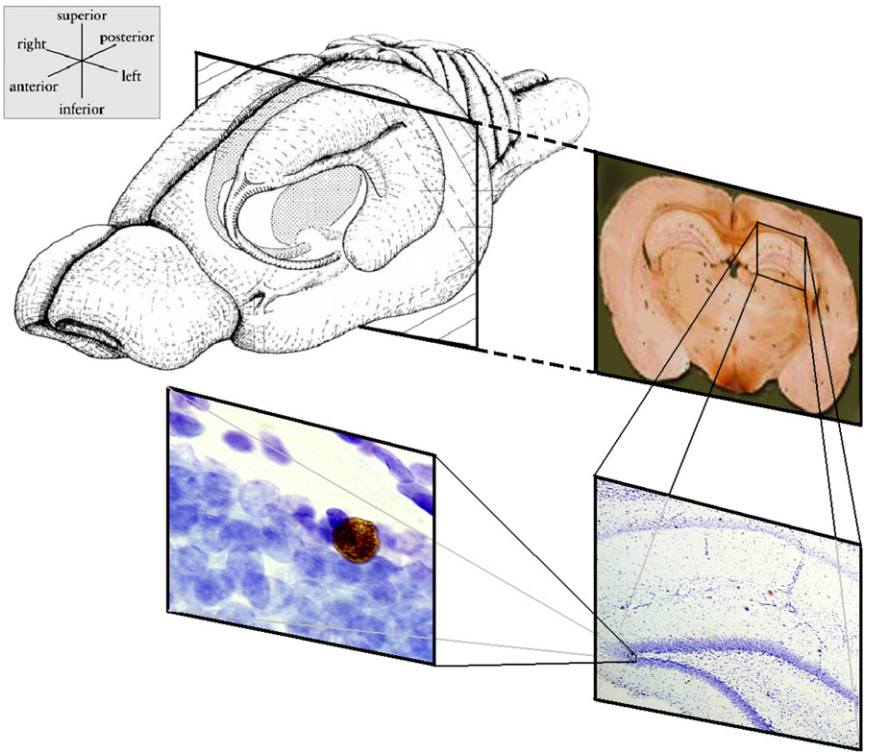

Figure 1. Orientation of the Rat Hippocampal Region

A drawing of a rat brain (top left; this image was published in *The Rat Nervous System*, George Paxinos, "Hippocampal Formation," p. 445, Copyright Elsevier [1995]) is used to show the location of the hippocampus. A coronal section through the dorsal hippocampus (top right) is presented with the granule cell layer in purple (bottom right). A newly generated cell (in dark brown) is shown among mature neurons (bottom left).

limited to those types that require the hippocampus for learning itself. This commentary will focus on the generation and survival of new neurons in the hippocampus with an emphasis on their response to learning. I will then turn to the question of whether new neurons are actually used for learning and/or whether they could be used in the storage or retrieval of memories for complex objects, situations, and concepts, such as those associated with our grandmothers.

Neural Stem Cells and Their Progeny

The term stem cell is generally meant to convey a cell that can renew itself and has no pre-established phenotype; that is, its progeny can adopt multiple lineages. Most of the new cells generated in the hippocampus are not literally stem cells but rather progenitor cells that arise from a population of cells that resemble stem cells and are often referred to as "neural stem cells." In brief, these neural stem cells give rise to progenitor cells that ultimately differentiate into neurons, at least in the hippocampus of adult mammals. "Neurogenesis" typically refers to the "birth," or generation, of new cells in the brain that become mature neurons with time. New neurons are not generated throughout the hippocampus but are rather generated specifically in one region—the dentate gyrus (Figure 1). As they mature, newly generated cells migrate short distances into the lower quadrant of the granule cell layer (Kempermann et al., 2003). In the first few days, these new cells develop dendrites and within a week begin to extend axons that synapse with pyramidal cells in area CA3 (Hastings and Gould, 1999; Piatti et al., 2006; Zhao et al., 2006). Over the course of a few weeks, they express molecular markers of immature neurons, followed by markers of mature neurons roughly a week later (Esposito et al., 2005). Within several more weeks, the new cells can produce action potentials and have thereby established themselves as functional neurons in the adult brain (van Praag et al., 2002).

Thousands of new cells can be produced in the hippocampus each day. However, across days and even hours, the numbers vary quite dramatically. First and foremost, the production of new cells is influenced by age (Cameron and McKay, 1999). Many more new neurons are generated before and during puberty than are generated in adulthood. By middle age, the numbers that are produced decrease significantly (Kempermann et al., 2003). The new cells are especially sensitive to changes in the internal environment, such as the presence of neurotransmitters. For example, antagonism of the NMDA type of glutamate receptor increases the numbers that are produced (Cameron et al., 1995). Also, an increase in the presence of serotonin either via antidepressants or more direct manipulations increases the production of new cells (Malberg et al., 2000). Changes in the external environment can also influence how many cells are produced. Animals that exercise or live in enriched environments produce more cells, whereas those exposed to stress or deprived of sleep produce significantly less (van Praag et al., 1999; Tanapat et al., 2001; Kempermann et al., 1997; Shors et al., 2007a). Perhaps more amazing is the effect of social dominance on cell number. Males that are higher in the hierarchy produce more than submissive males, and female rodents exposed to the pheromones of a dominant male produce more cells than when exposed to smells of a submissive male (Kozorovitskiy and Gould, 2004; Mak et al., 2007). Thus, the new cells are not only plentiful but also quite discriminating. In short, new cells in the adult brain are generally responsive to changes in their milieu, both the external and internal.

Proliferation versus Survival versus Rescue

Because so many new cells are generated in a structure that is intimately involved in learning (see below), it is tempting to speculate that neurogenesis is involved in the learning process itself. From this idea, two fundamental questions arise. First, does learning affect neurogenesis, and second, does neurogenesis (or its absence) affect the ability to learn? Nearly 10 years ago, we reported that learning does, in fact, impact neurogenesis (Gould et al., 1999), and soon thereafter, that neurogenesis might also be involved in learning (Shors et al., 2001). Since that time, many additional studies have appeared, some of which support

a relationship and others that do not. As with any new field, many of the conflicting reports arise due to challenges in establishing a consistent nomenclature. For example, the word neurogenesis can be used very broadly to refer to all stages of neuronal development from mitosis through maturation. Within this system are several distinct processes such as proliferation and survival. The word survival can also be used in different ways. In one sense, it defines the period of time over which a given cell lives. However, in the case of learning, the term can also relate to the likelihood that a given cell will survive to become a neuron. As noted, thousands of new cells are generated in the dentate gyrus each day. However, a relatively small percentage of those cells persist long enough to differentiate into mature neurons. Indeed, between about 1 and 2 weeks after their birth, as many as 60% perish (Gould et al., 1999). If one were to enhance cell production by exercise or antidepressants, more cells would be generated and more would tend to survive (in absolute numbers). But as a percentage of cells generated, it is not clear that the surviving fraction would increase. With learning, however, the percentage of cells that survive is increased (Gould et al., 1999). That is, if animals are trained when the cells are approximately 1 week of age, more of the newly born population survive. Therefore, the cells are essentially rescued from death by learning.

Once rescued from death by learning, most of the new neurons remain in the hippocampus for months at least (Leuner et al., 2004). Furthermore, most, if not all, of the cells that are available for rescue at the time of training are rescued (Waddell and Shors, 2008). Thus, learning has a large impact on the number of surviving neurons in the adult brain. That said, these cells are only rescued from death by a few types of learning tasks. One type is the associative learning task of trace conditioning. In this procedure, animals must learn to associate two events that do not occur together in time (Figure 2A). A second type is spatial maze learning. During this procedure, animals must learn to find a hidden platform using spatial cues in the environment (Figure 3). At first, it seemed as if the effects of learning on cell survival were limited to tasks that depend on the hippocampus for learning itself. This was a reasonable hypothesis because acquisition during both trace conditioning and spatial maze training depends on the hippocampus. Indeed, delay conditioning, a task that is very similar to trace conditioning but does not depend on the hippocampus for learning, does not rescue new neurons from death (Figure 2B) (Beylin et al., 2001). Similarly, training with a maze task that does not depend on spatial cues is not dependent on the hippocampus and does not rescue new neurons from death (Gould et al., 1999; Sisti et al., 2007; Drapeau et al., 2007) (Figure 3). Thus, it would appear that the new cells are especially responsive to learning tasks that depend on the hippocampus for learning itself. However, the effects of learning on cell survival are not entirely encapsulated by this dichotomy. For instance, learning a task known as latent inhibition does depend on the hippocampus, but learning the task does not rescue new neurons from death (Solomon and Moore, 1975; Waddell and Shors, 2008). Similarly, training with a trace conditioning task that does not require the hippocampus can rescue the new cells (Figure 2C) (Bangasser et al., 2006; Leuner et al., 2006). Clearly, simply classifying a task as hippocampal dependent or not is not sufficient to account for the effects of learning on neurogenesis in the adult brain.

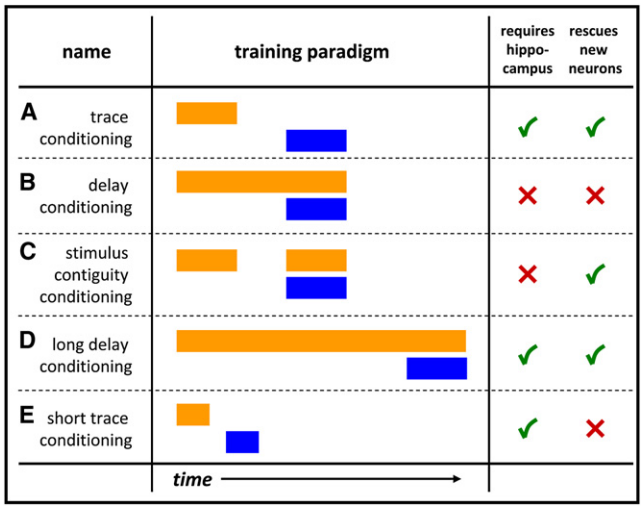

Figure 2. Training Methods Used in Classical Eyeblink Conditioning that Impact Neurogenesis

During trace conditioning (A), the conditioned stimulus (CS, orange) and unconditioned stimulus (US, blue) do not occur together in time. During delay conditioning (B), the stimuli overlap in time. Learning this task is not dependent on the hippocampus, and learning the task does not rescue new neurons from death. If the CS is presented again, after a temporal gap, with the US (C), the trace paradigm is also hippocampal independent but does rescue new neurons from death (Dalla et al., 2007). During very long delay conditioning (D), the stimuli still overlap in time, but because the interval between the two stimuli is especially long, learning does depend on the hippocampus. Training with this task does rescue new neurons from death (Leuner et al., 2006). In the short trace paradigm (E), the hippocampus is still involved, but learning this task did not increase the number of surviving cells (Shors et al., 2007b), perhaps due to the relative ease of the task.

If not this simple dichotomy, what then? It does appear that tasks that are more "difficult" to learn are more likely to increase the number of surviving cells. In general, we consider tasks as difficult to learn if more trials of training are necessary in order to reliably and accurately express a learned response. For example, learning to emit an eyeblink response during delay conditioning (which does not depend on the hippocampus) requires many fewer trials than learning to emit a similar eyeblink response during trace conditioning, which does depend on the hippocampus. If a typical delay conditioning task is rendered more difficult, learning this new task will rescue new neurons from death (Figure 2D) (Leuner et al., 2006). In contrast, if a trace conditioning task, which is usually quite difficult to learn, is made easier to learn, learning the new task does not increase the number of surviving cells (Figure 2E) (Shors et al., 2007b). In the end, it appears that tasks that are more difficult to learn are also more likely to rescue new neurons from death. But this is not the end of the story. It is also critical that the animals actually learn. That is, animals that learn best tend to possess more cells after training than those that are trained but do not learn or do not learn very well (Leuner et al., 2004; Dalla et al., 2007; Sisti et al., 2007; Drapeau et al., 2007). Of those animals that do learn, those that require more trials to do so tend to retain the most cells (Waddell and Shors, 2008). Together, the data suggest at least three factors are necessary to increase the number of cells that survive after training: first, the training conditions must be sufficiently challenging; second, some cognitive effort and/or engagement must take place; and finally, learning itself must occur.

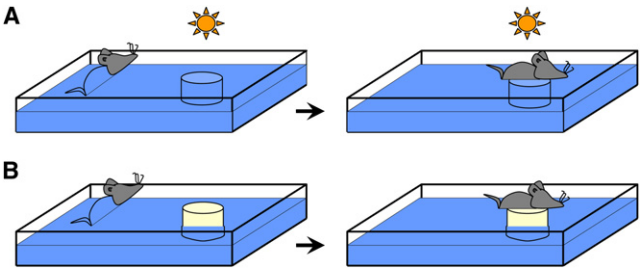

Figure 3. Spatial Tasks that Rescue New Neurons from Death
(A) In the Morris water maze, animals depend on external cues (orange burst) to locate a submerged and hidden platform. Learning to navigate in space using spatial cues depends on the hippocampus and rescues new neurons from death (Gould et al., 1999; Sisti et al., 2007). However, learning to find the hidden platform does not depend on the presence of new neurons (Shors et al., 2002).
(B) Learning to find the platform when it is visible does not require the hippocampus and does not rescue new neurons from death.

A Limited Role for New Neurons in Learning

The findings discussed above indicate that learning affects new neurons in the adult brain. They do not address the all-important question—are new neurons necessary for learning to occur? The types of learning that absolutely require the hippocampus tend toward those that require considerable effort and cognitive engagement—some call it awareness—to learn. Some of those processes include learning to associate events across time (trace conditioning), learning the sequence of events (relational learning), and learning to associate the environment with an event even though the environment is continually changing (contextual learning) (Fortin et al., 2002). The hippocampus also becomes critically engaged when animals must learn to navigate and remember locations in three-dimensional space without any obvious visual or olfactory cues to follow (spatial learning) (Riedel et al., 1999; O'Keefe and Nadel, 1978). The hippocampus is likewise involved in establishing new declarative memories, as well as the conscious recollection of events or episodes, so-called episodic memories (Cohen and Squire, 1980; Tulving, 2002; Bird and Burgess, 2008). On the face of it, the types of learning that require the hippocampus do not appear to have much in common. Despite numerous attempts to identify the common denominator, none are entirely satisfactory; as a consequence, we tend to classify learning tasks as hippocampal dependent or not. To be explicit, learning is dependent on the hippocampus if lesions to all of the neurons within it prevent or severely retard learning. Learning is not dependent on the hippocampus if learning still occurs even though all the neurons within the hippocampus do not exist (both old and new neurons).

Whether new neurons are necessary for learning to occur has proven a difficult question to answer convincingly, although a number of suggestive reports exist. In one such study, the generation of new cells was reduced by treating animals each day for 2 weeks with MAM, an antimitotic agent (Shors et al., 2001). After removal of the drug, animals were trained on a variety of learning tasks, including some that depend on the hippocampus and others that do not. Animals that were treated with the drug were generally unable to learn the associative memory task of trace conditioning, in which animals must learn to associate events across a gap in time. This effect occurred during training with either an eyeblink or a fear response (Shors et al., 2002). Thus, when neurogenesis was prevented, animals experienced a learning deficit when required to learn to associate discontiguous events across time, irrespective of which motor response was used to assess learning.

One argument levied against these findings is that because the antimitotic agent was injected peripherally over days, the proliferation of other nonneural cells was also prevented, which could contribute to performance deficits during training. This is certainly a valid argument that can not be disproved, but with some caution, it can be disputed. Specifically, animals treated with the antimitotic agent were able to learn most other tasks, including an eyeblink conditioning task that uses the same stimuli and requires emission of the same conditioned and unconditioned responses, i.e., delay conditioning (Figure 2B). As noted above, delay conditioning does not depend on the hippocampus for learning and is also quite easy to learn. In these studies, we found no evidence that the drug induces nonspecific effects on performance that could in turn influence learning abilities. For example, the animals expressed normal anxiety-related behaviors, pain sensitivity, and behavioral responses to the unconditioned stimuli (Shors et al., 2001, 2002).

During context conditioning, an animal learns about the environment in which an event occurs; typically, the event is an aversive experience. The formation of this type of association is generally dependent on the hippocampus (Kim and Fanselow, 1992). Nonetheless, animals can readily learn to fear a context even though they possess few new neurons (Shors et al., 2002). That said, there are reports of decrements in context conditioning after hippocampal irradiation. These data are compelling because irradiation tends to eliminate most of the new cells in the hippocampus (Winocur et al., 2006; Saxe et al., 2006). However, as in the use of antimitotic agents, irradiation treatment does have potential side effects that could affect performance while trying to assess learning in laboratory animals. In the meantime, new techniques are being developed that decrease neurogenesis without interfering with established neurons. One such study used a genetic approach to reduce the number of neural stem cells. In this case, there was no observable consequence on learning to fear a context that had been associated with a foot shock, i.e., context conditioning (Zhang et al., 2008). As a whole, multiple studies indicate that neurogenesis is not necessary to learn simple associations between aversive events and the context. New neurons may become more engaged as the associations with the environment become more ambiguous.

Dissociations between Spatial Learning and Neurogenesis

Oddly enough, animals with very few new neurons readily learn to navigate in the Morris water maze task (Figure 3) (Shors et al., 2002). I say oddly because learning this type of response is dependent on the hippocampus for both learning and memory (Riedel et al., 1999). It is also the most common laboratory procedure used to assess learning and memory in rodents. Other groups have found that animals can perform in the maze after irradiation—thus, in the near absence of any new neurons (Snyder et al., 2005; Saxe et al., 2006). Despite these apparent dissociations, there remains much speculation about neurogenesis and

spatial learning. Interestingly, one study did report a relationship with spatial memory rather than learning, per se. As before, irradiated animals readily learned to find the hidden platform using spatial cues but then had some difficulty remembering its location some weeks later (Snyder et al., 2005). This observation is potentially important because the hippocampus does appear to have a more long-lasting role in the retention and retrieval of spatial memory (Riedel et al., 1999). That said, others report that irradiated animals can remember the spatial location at a similar point in time; i.e., 2 weeks after training (Saxe et al., 2006).

Again, it is critical to distinguish between the effects of learning on neurogenesis and the role that new neurons may play in the learning process. Recall that spatial learning enhances the survival of the adult neurons that were born 1 week prior to the training experience (Epp et al., 2007; Gould et al., 1999). Moreover, the number of neurons correlated with the time it took for animals to find the platform 2 weeks later (i.e., memory for the platform location) (Sisti et al., 2007). Also, new cells are more likely than older, established, neurons to become activated during a spatial memory task (Kee et al., 2007). Although intriguing, all of these effects could occur whether or not the cells are necessary for learning to occur. To solidify this point, a recent study found that mice with a significantly reduced population of new neurons could find the platform in a water maze when it was located above the water and very visible (as would be expected, Figure 3B). However, as a consequence, these same animals were then able to find the platform when it was hidden under the water (Zhang et al., 2008). Thus, animals were able to use spatial cues and remember spatial location in the near absence of newly generated neurons. With few exceptions, we must accept the fact that animals can learn to navigate in space and emit the appropriate operant response, with very few if any new neurons.

Neurogenesis in Learning versus Memory

There has been much speculation about what the new cells do once they become incorporated as mature neurons into the hippocampus. Some groups argue that the numbers are too few to matter. This may be the case, but most of the cells that remain in the hippocampus after learning are still there 2 months later (Leuner et al., 2004). Within that time period, each neuron can develop thousands of spines (Zhao et al., 2006). Therefore, if tens of thousands of new neurons are generated each week, the number of potential connections could increase dramatically over a relatively short period of time. In addition, the new cells are located in a prime location—at the first major synapse in the hippocampal formation (see Figure 1). It is only logical that the additional neurons will impact neuronal activity within the dentate gyrus, not to mention efferent synapses and other brain regions. But the question asked here is whether the remaining neurons are then used to retrieve or otherwise recall the memory of the task by which they were rescued? On this point, it seems unlikely. First and foremost, the hippocampus is mostly involved in learning and only temporarily involved in the retention of most memories. Within just days of learning, animals without a hippocampus can clearly remember the context in which an aversive event occurred, and they readily express a memory for the trace interval (Kim and Fanselow, 1992; Takehara et al., 2002). If the hippocampus is not required to express these types of memory, then new neurons within the hippocampus cannot be necessary either, irrespective of any effect that learning may have on them.

Conclusion

In the end, we must conclude that new neurons are not grandmother cells in the intended sense of the word. Rather, given their experiential naiveté coupled with their prime geographical location, they seem more appropriate as templates for new learning. This idea, like most, is not new. Indeed, Fernando Nottebohm came to the same conclusion after decades of studying neurogenesis in the songbird. Specifically, he proposed that the generation of new neurons serves to replenish a circuit with cells that had yet to experience "learning" so that the subject could respond anew (Nottebohm, 2002). To me, this idea is as apropos for neurogenesis in the hippocampal formation as any proposed thus far. That is, new cells have the ability to respond anew to a learning experience without the challenge of distinguishing old from new. And yet, not just any sort of learning experience will do. In fact, one might recognize the intriguing similarity between learning the fine motor skills necessary to sing a bird song and those used to time a fine motor response like the eyeblink. Both skills require extensive practice time (i.e., many trials) to learn, and both tasks become refined within tens of milliseconds. However, as with most skill learning, not all individuals learn equally. In the case of bird song, those that learn successfully are more likely to defend their territory, gain access to females, and ultimately reproduce their genes. Perhaps in mammals, too, the relationship between learning and neurogenesis ensures more than just survival of the neuron.

The "rediscovery" of neurogenesis in the adult brain has generated much excitement in the field of biology—but no more so than in the field of stem cell biology. Much of that excitement is predicated on the hopes that stem cells might be used to restore learning and memory in humans with Alzheimer's disease (AD) and other debilitating conditions. Current evidence suggests that patients with dementia continue to produce new neurons in their hippocampus, but the numbers are few and most do not mature (Shors, 2003; Jin et al., 2004; Li et al., 2008). Of course, AD ravages many more neurons than just new ones in the dentate gyrus. Nonetheless, it is perhaps paradoxical that the few new neurons patients do produce may not survive simply because the individuals are not able to learn. Stem cell biologists might consider how learning rescues new neurons from death in healthy brains as they attempt to restore learning and memory to those individuals who have lost this most essential feature of life.

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